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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/715,229	11/17/2003	Tariq M. Rana	UMY-041RCE	5733

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EXAMINER	
CHONG, KIMBERLY	
ART UNIT	PAPER NUMBER
1635	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/02/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/715,229	RANA, TARIQ M.	
	Examiner	Art Unit	
	Kimberly Chong	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 February 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-34* is/are pending in the application.

4a) Of the above claim(s) *18-34* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 02/15/2007 has been entered.

Status of Application/Amendment/Claims

Applicant's response filed 02/15/2007 has been considered. Rejections and/or objections not reiterated from the previous office action mailed 08/15/2006 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

With entry of the amendment filed on 02/15/2006, claims 2-34 are pending in the application. Claims 2-17 are currently under examination.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 2-8 and 10-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ecker et al. (US Patent No. 5,965,722), Hojo et al. (Eur Respir J, 1998), Hammond et al. (Nature Reviews Genetics, 2001), Bass et al (Nature, 2001) and Tuschl et al. (cited on PTO Form 892 filed 11/15/2005).

The claims are drawn to a siRNA comprising a sense strand and an antisense strand wherein the antisense strand comprises a modified base positioned opposite at least one pint mutation in the first allele and wherein the modified base is capable of enhancing binding interactions, wherein the sense strand comprises a sequence homologous to a mutant allele encoding a gain-of-function mutant protein, wherein the modified base is selected from the group as listed in claim 4, wherein the point mutation is an adenine or thymine, wherein the siRNA targets a disorder such as ALS, Huntington's, Alzheimer's or Parkinson's, wherein the siRNA is from 10-50, 20-40, 18-25 nucleotides in length an drawn to a composition and a host cell comprising said siRNA.

Ecker et al. teach antisense compounds targeted to a mutated Ras gene and teach said antisense compounds are a useful tool for understanding the role of various oncogenes (see column 3). Ecker et al. teach antisense compounds comprising modified nucleotide bases increase the affinity for base mismatches in mutated genes and further enhance the compounds selectivity for such mutated genes (see column 3). Ecker et al. teach a single nucleotide mutation is responsible for mutated Ras protein

expression (see column 3). Ecker et al. teach incorporation of a 2'amino adenine at the position that is complementary to the uracil of the mutated codon serves to stabilized the hybridization of the antisense oligonucleotide to the mutated gene (see column 21, lines 40-45). Ecker et al. further teach incorporation of a 2,6-diamino adenosine complementary to the uracil of the mutated codon was also found to be effective in increasing the hybridization of the antisense compound to the mutated gene (see column 21, lines 55-65). Ecker et al. teach compositions comprising said antisense compound that are useful for therapeutic applications and further teach expression of said antisense compounds in cells (see column 22). Ecker et al. do not teach siRNA targeted to a mutated gene and do not teach the point mutation is an adenine or thymine.

Hojo et al. teach a common problem with diseases such as lung cancer are found to be due to overexpression of the p53 and further teach overexpression of p53 is due to point mutations of the p53 gene wherein the mutations are commonly an adenine or a thymidine.

Hammond et al. teach two methods for silencing specific genes: antisense and RNA interference. Hammond et al. teach that although antisense methods are straightforward techniques for probing gene function, the methods have suffered from "...questionable specificity and incomplete efficacy." (see page 110, column 1). Hammond et al. further teach " "...dsRNAs have been shown to inhibit gene expression in a sequence-specific manner" and further "RNAi is a potent method, requiring only a few molecules of dsRNA per cell to silence expression." Similarly, Bass et al. states

that RNA interference using siRNA has "...repeatedly proven itself to be more robust than antisense techniques: It works more often, and typically decreases expression of a gene to lower levels, or eliminates it entirely." Bass et al. points out that siRNAs are effective at targeting transgenes as well as naturally occurring endogenous genes (see page 428). Bass et al. further states "...siRNAs are effective at concentrations that are several orders of magnitude below the concentrations typically used in antisense experiments."

Tuschl et al. teach chemically synthesized siRNA molecules that mediate RNA interference. Tuschl et al. teach a 21 nucleotides siRNA wherein each separate strand comprises at least 19 nucleotides complementary to the nucleotides of the other strand and teach compositions comprising siRNA and an acceptable carrier (see page 9, lines 17-25). Tuschl et al. teach that siRNAs represent a new alternative to antisense or ribozyme therapeutics. Tuschl et al. teach the siRNA may contain at least one modified analogue, such as a modified base wherein the modified base comprises 5-bromouracil or 5-iodouracil, and the modification may be located at positions that do not interfere with RNAi mediating activity.

It would have been obvious to one of skill in the art to make a siRNA targeted to a mutated gene comprising a point mutation that is responsible for proliferation of cells leading to cancer. It would have been further obvious to one of skill in the art to target a p53 gene for treatment of cancer.

One of skill in the art would have been motivated to make a siRNA targeted to a mutated gene wherein the antisense strand comprises a modified base because Ecker

et al. teach incorporation of modified bases increase the specificity of the nucleic acid to the mismatched base. One of skill in the art would have been motivated to incorporate modifications to siRNA to improve the affinity for target genes because siRNA encounters similar problems as other nucleic acid based therapies. One of skill in the art would have been further motivated to make a siRNA targeted to a mutated p53 because Hojo et al. teach that overexpression of p53 is responsible for the complications in lung cancer and one would have been motivated to decrease the expression of p53. Hojo et al. demonstrates, for example, that it is the nature of the mutated target that would determine the base that is opposite the modified base of the nucleic acid based drug.

Ecker et al. provide evidence that one of skill in the art would have had a reasonable expectation of inhibiting a mutant target gene and given that Tuschl et al. teach how to make and use any siRNA targeted to any gene, Hammond et al. and Bass et al teach siRNA are preferred over antisense compounds, one would have had a reasonable expectation of success at making a siRNA targeted to a mutated gene.

Thus, in absence of evidence to the contrary, the invention would have been prima facie obvious to one of skill in the art.

Claims 2-5, 7 and 9-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ecker et al. (US Patent No. 5,965,722), Hammond et al. (Nature Review Genetics, 2001), Bass et al (Nature, 2001) and Tuschl et al. (cited on PTO Form 892 filed 11/15/2005) and Xu et al. (cited on PTO Form 892 filed 11/15/2005).

The claims are drawn to a siRNA comprising a sense strand and an antisense strand wherein the antisense strand comprises a modified base positioned opposite at least one pint mutation in the first allele and wherein the modified base is capable of enhancing binding interactions, wherein the sense strand comprises a sequence homologous to a mutant allele encoding a gain-of-function mutant protein, wherein the modified base is selected from the group as listed in claim 4, wherein the point mutation is an adenine or thymine, wherein the siRNA targets a disorder such as ALS, Huntington's, Alzheimer's or Parkinson's, wherein the siRNA is from 10-50, 20-40, 18-25 nucleotides in length an drawn to a composition and a host cell comprising said siRNA.

Ecker et al. teach antisense compounds targeted to a mutated Ras gene and teach said antisense compounds are useful tools for understanding the role of various oncogenes (see column 3). Ecker et al. teach antisense compounds comprising modified nucleotide bases increase the affinity for base mismatches in mutated genes and further enhance the compounds selectivity for such mutated genes (see column 3). Ecker et al. teach a single nucleotide mutation is responsible for mutated Ras protein expression (see column 3). Ecker et al. teach incorporation of a 2'amino adenine at the position that is complementary to the uracil of the mutated codon serves to stabilized the hybridization of the antisense oligonucleotide to the mutated gene (see column 21, lines 40-45). Ecker et al. further teach incorporation of a 2,6-diamino adenosine complementary to the uracil of the mutated codon was also found to be effective in increasing the hybridization of the antisense compound to the mutated gene (see

column 21, lines 55-65). Ecker et al. teach compositions comprising said antisense compound that are useful for therapeutic applications and further teach expression of said antisense compounds in cells (see column 22). Ecker et al. do not teach siRNA targeted to a gene correlated with a disease selected fro ALS, Huntington's disease, Alzheimer' disease or Parkinson's Disease.

Hammond et al. teach two methods for silencing specific genes: antisense and RNA interference. Hammond et al. teach that although antisense methods are straightforward techniques for probing gene function, the methods have suffered from "...questionable specificity and incomplete efficacy." (see page 110, column 1). Hammond et al. further teach " "...dsRNAs have been shown to inhibit gene expression in a sequence-specific manner" and further "RNAi is a potent method, requiring only a few molecules of dsRNA per cell to silence expression." Similarly, Bass et al. states that RNA interference using siRNA has "...repeatedly proven itself to be more robust than antisense techniques: It works more often, and typically decreases expression of a gene to lower levels, or eliminates it entirely." Bass et al. points out that siRNAs are effective at targeting transgenes as well as naturally occurring endogenous genes (see page 428). Bass et al. further states "...siRNAs are effective at concentrations that are several orders of magnitude below the concentrations typically used in antisense experiments."

Tuschl et al. teach chemically synthesized siRNA molecules that mediate RNA interference. Tuschl et al. teach a 21 nucleotides siRNA wherein each separate strand comprises at least 19 nucleotides complementary to the nucleotides of the other strand

and teach compositions comprising siRNA and an acceptable carrier (see page 9, lines 17-25). Tuschl et al. teach that siRNAs represent a new alternative to antisense or ribozyme therapeutics. Tuschl et al. teach the siRNA may contain at least one modified analogue, such as a modified base wherein the modified base comprises 5-bromouracil or 5-iodouracil, and the modification may be located at positions that do not interfere with RNAi mediating activity.

Xu et al. teach allele-specific RNA interference of mutated genes comprises administering a siRNA targeted to the mutant gene. Xu et al. teach that certain types of human disease, such as ALS, Huntington's disease, Alzheimer' disease or Parkinson's Disease are caused by dominant gain-of-function mutations and because the wild-type gene often performs important functions compared to the toxic effects of the mutant gene, it would be advantageous to selectively inhibit the mutated gene (see Abstract and paragraph 0009).

It would have been obvious to one of skill in the art to make a siRNA targeted to a mutated gene comprising a point mutation that is responsible for proliferation of cells leading to cancer. It would have been further obvious to one of skill in the art to target a p53 gene for treatment of cancer, as taught by Hojo et al. Further, one of skill in the art would make a siRNA targeted to a dominant gain-of-function mutation, as taught by Xu e al.

One of skill in the art would have been motivated to make a siRNA targeted to a mutated gene wherein the antisense strand comprises a modified base because Ecker et al. teach incorporation of modified bases increase the specificity of the nucleic acid to

the mismatched base. One of skill in the art would have been motivated to incorporate modifications to siRNA to improve the affinity for target genes because siRNA encounters similar problems as other nucleic acid based therapies. One of skill in the art would have been further motivated to make a siRNA targeted to a mutated p53 because Hojo et al. teach that overexpression of p53 is responsible for the complications in lung cancer and one would have been motivated to decrease the expression of p53. Moreover, one of skill in the art would have been motivated to specifically target disorders such as ALS, Huntington's disease, Alzheimer' disease or Parkinson's Disease because Xu et al. teach siRNA are effective at silencing mutating gene expression compared to the wild-type expression.

Ecker et al. provide evidence that one of skill in the art would have had a reasonable expectation of inhibiting a mutant target gene and given that Tuschl et al. teach how to make and use any siRNA targeted to any gene, Hammond et al. and Bass et al teach siRNA are preferred over antisense compounds, one would have had a reasonable expectation of success at making a siRNA targeted to a mutated gene. One of skill in the art would have had a reasonable expectation of success at targeting a gene responsible for disorders such as ALS given than Xu et al. teach a specific embodiment of selective targeting a mutant gene of ALS while not targeting the wild-type gene.

Thus, in absence of evidence to the contrary, the invention would have been prima facie obvious to one of skill in the art.

Response to Applicant's Arguments

Re: Claim Rejections - 35 USC § 112

The rejection of claims 3-17 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is maintained for the reasons of record filed 08/15/2006.

Applicant's arguments are considered but are not persuasive. Applicants reiterate their previous arguments set forth in the previous response filed 05/15/2006. It appears applicants position is that they are in fact in possession of the instantly claimed invention because "the specification provides extensive guidance for designing and selecting siRNAs which can be used for allele-specific cleavage" and "provide a plethora of explicit examples of diseases caused by dominant, gain-of-function gene mutations." Applicants further state that because of this guidance in the specification for how to test and select siRNA molecules that direct allele-specific cleavage and because such techniques were routine to one of skill in the art at the time of filing, one of skill in the art would now how to generate a siRNA targeted to a particular mRNA to directed allele-specific targeting. These arguments are not convincing.

As stated in the previous Office action filed 08/15/2006, although the specification adequately describes siRNA compounds targeted to cells expressing reporters GFP and RFP (see Examples 1-3), by fully setting forth their sequence and function, and by describing the materials and methods needed to measure their activity, adequate written description does not exist for the virtually unlimited number of other siRNA in the claimed genus that target any mutant allele from any specie.

Further, despite the examples of disease caused by dominant, gain-of-function mutations and the general guidelines provided by application, one of skill in the art cannot readily extrapolate these general teachings provided in the specification to adequately describe the entire genus of siRNA targeting any mutant gene that would *direct cleavage* of mRNA encoded by the mutant gene because the art teaches variability within the genus, and the species described do not fairly represent that variability.

It was well known at the time of filing of the instant application that variability exists within the genus. Holen et al. (Nucleic Acids Res 2002 of record on PTO 892), for example, report that siRNAs directed against the same target varied widely in their silencing efficiencies (pp. 1759-1760). "...despite the minimal sequence and position differences between these siRNAs, they displayed a wide range of activities" (page 1758). "Our results indicate that susceptible siRNA target sites in some human genes may be rare."(page 1765). "At present, however, the factors determining the differences in siRNA efficiency remain unclear." (page 1761).

The specification does not provide adequate written description of a siRNA targeted to any sequence comprising point mutations and that *directs allele-specific cleavage of an mRNA encoded by any mutant allele* and the art clearly recognizes that target sequence is a critical parameter and that the design of siRNA is crucial for the success of gene expression inhibition using siRNA. Further, the art does not provide a core structure or motif that would function in directing allele-specific cleavage of any

mutant allele and therefore one is left to empirically screen for siRNA compounds of the invention.

Thus, the instantly claimed invention cannot be said to have been adequately described in a way that would convey with reasonable clarity to those skilled in the art that, as of the filling date sought, applicant was in possession of the claimed invention.

Re: Claim Rejections - 35 USC § 102

The rejection of record of claims 1-2, 4-5 and 10-17 under 35 U.S.C. 102(e) as being anticipated by Tuschl et al. (WO 02/44321) is withdrawn in response to Applicant's arguments in the response filed 02/15/2007.

Re: Claim Rejections - 35 USC § 103

The rejection of record of claims 3-5, 7 and 9 under 35 U.S.C. 103(a) as being unpatentable over Xu et al. (US 2004/0192629) in view of Buhr et al. (6,476,205) is withdrawn in response to Applicant's arguments in the response filed 02/15/2007.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kimberly Chong whose telephone number is 571-272-3111. The examiner can normally be reached Monday thru Friday between 7-4 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Schultz can be reached at 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public. For more information about the PAIR system, see http://pair-direct.uspto.gov.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Kimberly Chong
Examiner
Art Unit 1635